2vp

NASA TECHNICAL TRANSLATION NASA TT F-15,369

ACUTE BLOOD LOSS

V. B. Koziner

(NASA-TT-F-15369) ACUTE BLOOD LOSS N74-19721
(Techtran Corp.) 33 p HC $4.75 CSCL 06E

Unclas
G3/04 32706

Translation of:
Patologicheskaya Fiziologiya Ekstremal'nykh
Sostoyaniy [Pathological Physiology of Extreme Conditions],
Edited By P. D. Gorizontov and N. N. Sirotinin, Moscow,
"Meditsina" Press, 1973, pp. 160-179.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D. C. 20546 MARCH 1974

STANDARD TITLE PAGE

1. Report No. NASA TT F-15,369	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle ACUTE BLOOD LOSS		5. Report Date MARCH 1974
		6. Performing Organization Code
7. Author(s) V. B. Koziner		8. Performing Organization Report No.
		10. Work Unit No.
9. Performing Organization Name and Address Techtran Corporation P.O. Box 729, Glen Burnie, Md. 21061		11. Contract or Grant No. NASw-2485
		13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of: Patologicheskaya Fiziologiya Ekstremal'nykh Sostoyaniy [Pathological Physiology of Extreme Conditions], Edited By P. D. Gorizontov and N. N. Sirotinin, Moscow, "Meditsina" Press, 1973, pp. 160-179.

16. Abstract

A description of the physiology and treatment of various types of blood loss. Characterization of the varying stages of blood loss by severity. Suggestions as to drugs which are indicated and contraindicated during blood loss. A discussion of the efficacy of blood replacing substances and plasma. An account of various experiments carried out on animals to determine the effective blood loss and the tolerance of the organism to blood loss. An evaluation of the current state of blood transfusion practice.

17. Key Words (Selected by Author(s))	18. Distribution Statement Unclassified-Unlimited

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	~~31~~ 33	$4.75

NASA-HQ

ACUTE BLOOD LOSS

V. B. Koziner[1]

The loss of a significant amount of blood can be due to various causes: /160*
injury of the blood vessels, their destruction by a pathological process (gastric ulcer, intestinal ulcer, atherosclerosis, tuberculosis, varicose distention of the veins, etc.), by destruction of capillaries, and disruption of the blood's coagulating system, when slight injury to a blood vessel can lead to lethal blood loss. Hemorrhages in obstetric practice, which can be caused by poor contraction of the uterus after births or by an extremely low content of fibrinogen in the blood, occupy a particular place. Dependent upon cause, hemorrhage can be either external or internal; the latter is particularly difficult for diagnosis in a case in which blood flows into the tissues.

Of great significance for prognosis and treatment are the amount of lost blood and the rate of its flow, but the volume of blood loss does not always determine the severity of the patient's condition. The preceding condition plays an important role: excessive fatigue, excessive cooling or overheating, trauma, shock, accompanying diseases, etc. The significance of age and sex is also great. All of the enumerated factors render an estimate of the severity of blood loss in the patient in a study of its influence on the organism extremely difficult. It would seem that this question could very easily be investigated in experiments carried out on animals, where one could exclude a number of factors and study the phenomenon in a purer form. However, an attentive acquaintance with experimental studies shows that even they frequently cannot provide an answer to the questions posed. Tolerance to blood loss is not identical in different animals. An estimate of the severity of blood loss is frequently made arbitrarily or according to the arterial pressure, or according to the decrease in volume of the circulating blood, and the latter is not always calculated accurately. There are studies where these indices are

[1] Doctor of Medical Sciences.
*Numbers in the margin indicate pagination in the foreign text.

even ignored and where the volume and severity of blood loss are not indicated. It is not surprising that even the results of experimental investigations frequently prove to be impossible to compare.

It has at present been established that for man the loss of approximately 50% of the blood is dangerous to life, while loss of more than 60% is absolutely lethal if reanimatologists do not rapidly intervene. A. V. Gulyayev established that if as the result of blood loss the volume of circulating blood /161 becomes less than 58 ml/kg, and the volume of erythrocytes becomes less than 10 ml/kg, the condition is incompatible with life.

As was stated above, the volume of blood loss does not always determine its severity, and for many cases blood loss can be lethal even with a quite small volume of lost blood, particularly in the case of injuries to the large main blood vessels.

Of the subject animals, dogs are extremely tolerant to blood loss. According to the data of Wiggers (1950), the loss of blood up to 30 ml/kg is compensated for by the dogs independently, without therapeutic aid. Allen et al., (1959) considers blood loss of 66% on the average (62-74%) of the volume of circulating blood to be lethal for the dog. According to our data, loss of 70% of the earlier measured volume of the circulating blood, which comprises 50-70 ml/kg, is absolutely lethal for the dog. For the cat, this figure will be smaller (40-50 ml/kg). Rabbits are even less resistant to blood loss. According to the data of Strawitz et al. (1961), the lethality for rats in which blood loss comprise 4% of body weight fluctuated from 20-70%. Establishing the exact boundary of lethal blood loss for animals, when the organism cannot compensate for it independently, can have great practical significance in experimental therapy when estimating different methods of treatment.

Hemodynamic Disorders

The primary reaction to blood loss will be vascular spasm (arteriole spasm), which occurs reflexively as the result of stimulation of the receptor vascular zones and an increase in tonus of the sympathetic nervous sytem. Therefore, with a small degree of blood loss, particularly if it occurs slowly, one can successfully maintain a normal level of arterial pressure. The latter was clearly shown by I. R. Petrov (1947), who observed a decrease in arterial pressure of 6% during slow letting of approximately 25% of the blood volume, while at the same time rapid loss of only 5% of the blood caused a decrease in arterial pressure of 13%. Unfortunately, it is very difficult to establish exact relationships between the volume of circulating blood which has remained in the organism, the amount of blood loss and arterial pressure, while one can only very approximately calculate the amount of blood remaining in the organism during very severe blood loss, and even more so for lethal blood loss. The fact of the matter is that all modern methods of determining the volume of circulating blood are based on assumptions that indicators added to the blood mix with it uniformly, which of course cannot be expected during severe blood loss when there is sharp disruption of circulation.

In recent years it has been established that there is no significant blood deposition in a healthy man. At the same time, blood loss causes deposition of part of the blood; consequently, the volume of circulating blood decreases to a greater value than could be expected. Surgeons introduced the concept of "total blood loss", understanding by this term the sum of lost and deposited blood, and in accordance with this they recommend transfusing blood in an amount twice as great as that which has been lost by external hemorrhage (P. P. Bulgakov, 1961; S. P. Markin, V. P. Strekalovskiy, 1967).

A consequence of a decrease in the volume of circulating blood will be a decrease in the venous influx to the heart. A hastening of the cardiac rhythm in the initial stages of blood loss to a certain extent supports cardiac output, but subsequently it unswervingly falls (Guyton et al., 1958). In experiments carried out on dogs with extremely severe blood loss, when the protective /162
strengths of the organism are exhausted, a decrease in cardiac output of almost ten times was recorded with a decrease of arterial pressure to 0-5 mm (V. B. Koziner, V. I. Korol'kov, 1969).

In addition to a hastening of the cardiac rhythm, there is an increase in the strength of cardiac contractions. Figure 38 shows a recording of pressure in the carotid artery and left ventricle of the heart of a rabbit at the onset of slow blood loss. Pressure in the left ventricle increases for a certain period of time while the systemic arterial pressure decreases. The observed increase in pressure in the chamber of the left ventricle indicates an increase in its contractions and more complete driving of blood from the heart. In experiments performed on dogs by the method of X-ray kimography, it was established that during lethal blood loss, when the arterial pressure is zero, in approximately one-half the animals there was still a compensative reaction which was expressed in an increase in the strength of cardiac contractions and in a decrease of residual blood in the ventricles. In other dogs compensation was absent and the residual blood in the ventricles was not utilized (I. B. Gurevich, M. L. Garfunkel', 1959; I. B. Gurevich, V. B. Koziner, 1962). These experiments show that during a decrease in arterial pressure to zero, the reserve strength of the heart is exhausted to a dissimilar extent among all animals. The latter has significance for therapy and prognosis.

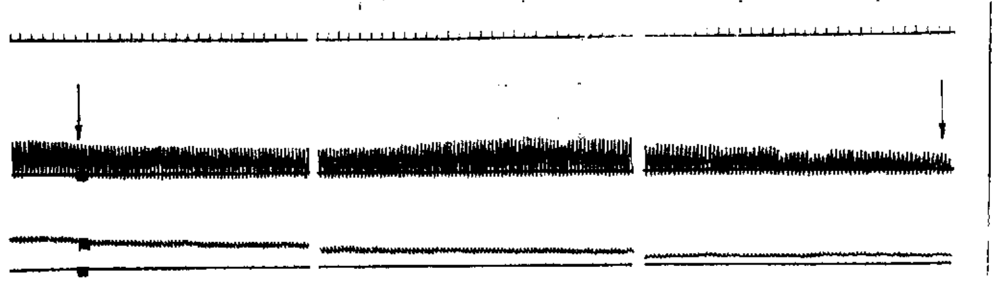

Figure 38. Pressure in the Left Ventricle of the Rabbit with Blood Loss of 20 ml/kg. Recording on the mingograph. From top to bottom: time mark (1 second); pressure in the chamber of the left ventricle and zero line for it. Systemic arterial pressure in zero line for it. Arrows denote the onset and termination of blood loss.

The reaction of the coronary blood vessels to blood loss has its own characteristics. According to the data of Pantzer and Shumacker (1961), in dogs, with a decrease in arterial pressure to 70%, the coronary blood flow decreases by only 50%. In unique experiments (V. B. Koziner, 1963), conducted on cats, it was established at the very onset of blood loss, when arterial pressure decreases only by a small value, the volume of coronary blood flow does not change.

Subsequently, proportional to a decrease in arterial pressure, there is also a decrease in the volume of coronary blood flow but to a lesser degree.

Thus, with a decrease in arterial pressure to 50% of the original level, the coronary blood flow decreases by only 30%. At the end of blood loss, when arterial pressure comprises 20% of the original level, coronary blood flow is equal to 40% of the original level. In certain experiments, even with a decrease in pressure in the carotid artery to zero, coronary blood flow was still maintained. Yu. V. Kofanova (1965), in experiments carried out on cats, observed a decrease in coronary blood flow of 10 times with blood loss of 50-60 ml/kg and with arterial pressure new zero. In other experiments performed on /163
dogs, with a decrease in arterial pressure of 10 fold, coronary blood flow decreased only 3 fold (V. I. Korol'kov, V. B. Koziner, 1966).

Changes in the electrocardiogram during blood loss are characteristic for progressing hypoxia of the myocardium and have been described in detail by many authors (V. A. Negovskiy, 1960, 1966 and others). They are expressed in a hastening of the rhythm at the beginning of blood loss and a decrease in it at the end, in a decrease in voltage of the R spike, inversion and increase in voltage of the T spike, drop in the S-T segment and conductivity disruption of varying degrees. The latter has greatest significance for evaluating the electrocardiographic data, inasmuch as the degree of coordination of the heart's work depends upon the conductivity function.

In experiments carried out on dogs, V. B. Koziner and V. I. Korol'kov (1968) made a comparison of the degree of oxygen pressure in the myocardium (pO_2) and changes in the EKG. With blood loss of 10 ml/kg, a slight decrease in arterial pressure was noted with a hastening in the rhythm of contractions, while the remaining indices did not change. With a decrease of pO_2 to 90% of the original level, which occurred at a blood loss of 20 ml/kg, the first signs of EKG changes appeared in the form of a decrease in the R spike. Blood loss of 30 ml/kg caused a decrease in pO_2 to 75% of the original level, and here the R spike continued to decrease, the T spike changed its direction and shape and the interval between P-Q began to lengthen. From this moment, further decrease in pO_2 is accompanied by progressive lengthening of the intracardiac conductivity. With oxygen pressure of about 60% of the original level (blood loss of 40 ml/kg), there is a significant slowing of the auricle-ventricular conductivity up to the point of appearance of partial or total blockade, and the S-T segment is depressed. The critical value is a pO_2 of about 50% of the original value. Changes in the EKG here show a picture of different degrees of disruption of rhythm and conductivity: rhythm can be sinusoidal, atrio-ventricular, ideo--ventricular, and extrasystoles, monophase oscillations, partial or complete transverse blockade, increase or decrease in the Q-T spike with discontinuity of the P and R spikes and a giant T spike are observed. Such change, obviously, is caused by the characteristics of myocardial metabolism caused by the individual resistance of the heart to hypoxia, and also by different times of action of hypoxia. With a subsequent decrease in pO_2, or with long-term stay under conditions of such low oxygen pressure, the agonal period begins. During this time one occasionally observes short-term increase in tonus of the sympathetic nervous system which is manifested in restoration of the sinusoidal rhythm, hastening of the cardiac contractions and slight elevation of arterial pressure.

With blood loss, redistribution of the blood and blood flow in various vascular regions change differently. Interesting investigations were conducted on rats using radioactive rubidium, by the aid of which success was attained in determining the value of cardiac output and distribution of blood throughout the organs. With blood loss of 10 ml/kg, cardiac output decreased by 50%. Here the influx of blood to the brain and adrenals did not change while blood flow to all other organs diminished. To a great extent, the drop was felt in the kidneys, skin, and muscles. With blood loss of 21-25 ml/kg, arterial pressure decreased to 28 mm Hg while cardiac output *in toto* comprised 15% of the original value. There was a significant decrease in coronary blood flow, and blood supply to the brain began to be disrupted; there was a powerful increase in resistance in the blood vessels of the kidneys, of the internal organs and skin, while in the muscles no such increase was observed. The latter made it possible to hypothesize that it is in fact in the muscles and /164
not in the internal organs that blood accumulates in the later stages of blood loss, when blood flow is sharply reorganized (Sapirstein et al., 1960). Similar data were obtained by Nentze et al. (1968) in experiments carried out on rabbits with blood loss of 28 ml/kg, and by Abel and Murphy (1962) in experiments carried out on dogs with blood loss of 20 ml/kg.

During extreme degrees of blood loss, pressure in the blood vessels of the circle of Willis falls more slowly at a certain stage than it does in the aorta (Figure 39). The latter indicates the presence of a particular locking mechanism in the regional arteries of the brain, by the aid of which the brain is locked out of the systemic circulation during a sharp decrease in systemic arterial pressure, as the result of which the capillaries of the systemic circulation can sustain a reduced blood volume for several minutes (G. I. Mchedlishvili, 1968). At the same time as resistance gradually increases in the main blood vessels of the brain, the arteries of the soft membrane of the brain expand and pressure in the venous sinuses decreases (G. V. Amashukeli, 1969). Proportional to the outflux of blood, there is a decrease in the volume and pulsation of the brain and its respiration fluctuations disappear, indicating a decrease in the supply of blood to the brain; but it is only necessary to cease blood loss, and blood supply to the brain will independently reestablish itself, even though arterial pressure remains diminished (Figure 40). This peculiarity of the blood supply of the brain is /165 also reflected in its oxygen supply. Figure 41 shows a recording of pO_2 in the cerebral cortex. In this experiment, cessation of blood loss alone also led to reestablishment of pO_2 in the brain tissues.

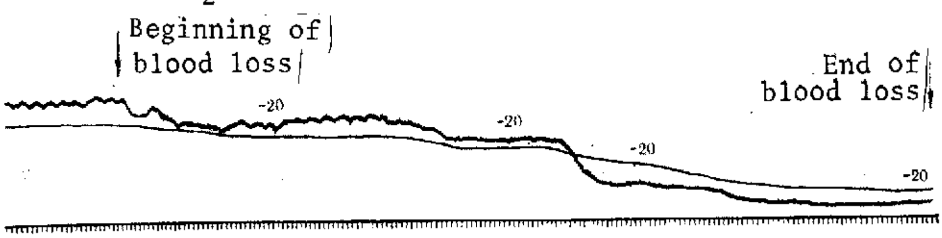

Figure 39. Spasm of the Regional Arteries of the Brain During Blood Loss. Experiment performed on a rabbit weighting 4 kg. Recording on kimograph. From top to bottom: pressure in the aorta; pressure in the circle of Willis; zero line, same line notes time (5 seconds). Minus figures - amount of lost blood (in milliliters). During the time of blood loss spasm of the regional arteries of the brain appeared and pressure in the circle of Willis was greater than in the aorta.

Significant disorders in renal circulation during acute blood loss cause a decrease in diuresis, while a drop in arterial pressure below 40 mm Hg leads to cessation of urine formation due to hydrostatic pressure in the capillaries becoming lower than oncotic pressure of plasma. According to the data of G. V. Kovalevskiy (1963), reduced circulation in the kidneys during extremely severe blood loss is maintained in the vessels of the cortico-medullary region (juxtamedullary shunting), at the same time as the interlobular arteries and afferent arterioles of the glomeruli are in a state of spasm.

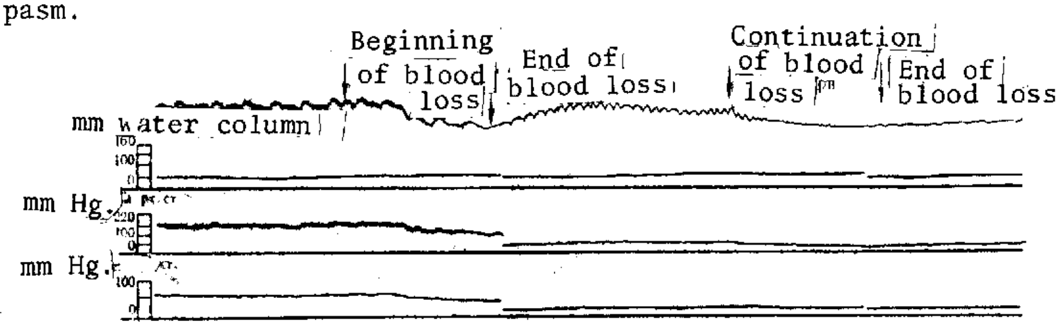

Figure 40. Volume and Pulsation of the Dog's Brain. Recording on the oscillograph. From top to bottom: volume and pulsation of brain; pressure in the jugular vein and zero line for it; pressure in the aorta and zero line for it; pressure in the circle of Willis and zero line for it.

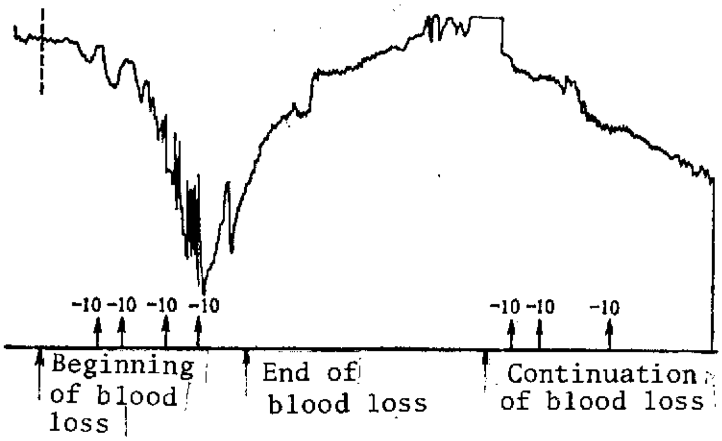

Figure 41. Oxygen Pressure in the Cerebral Cortex During Blood Loss. Experiment performed on a dog weighing 20 kg. Recording by the aid of direct current amplification with an ink recording device. (after Ye. A. Kovalenko and V. B. Koziner). Upper curve - pO_2, lower curve - zero line. Minus figures - - amount of lost blood (ml/kg).

As is known, up to 80% of the volume of circulating blood is located in the so-called low pressure system, i.e., in the veins and in the lesser circuit. In this system there are large reservoirs for blood: the cutaneous blood vessels, the large veins, the internal veins, the pulmonary blood vessels, and the chambers of the heart. During blood loss there is a contraction in the volume of these reservoirs. Hence, there can be a compensative decrease up to 10% of the volume of circulating blood without altering the work of the heart or the arterial pressure. Diminishing the size of the spleen in man does not play a great role and can only yield an additional 50 ml of blood (Freeman, 1963).

The normal volume of perfusion of tissues and arterial pressure are maintained here as a result of redistribution of the blood within the vascular system and transfer of part of the blood from the low pressure system to the high pressure system. As a result there is a slight decrease in venous pressure. With small blood losses this decrease has great significance in therapeutic practice for venous hypertonies, where even blood letting of 100-150 ml causes a decrease of venous pressure of 10-15 mm water column, while a loss of 300-400 ml leads to a decrease of from 40-70 mm water column. The favorable effect of bleeding during venous stenoses and edemas is based upon this; it /166
also has a favorable effect with pulmonary edema (R. A. Dymshits, 1958).

Over the course of a long period of time, disruption of circulation with blood loss was studied in the entire organism or in the large blood vessels of specific vascular regions, while at the same time circulation in the small blood vessels, directly nourishing the tissues, was inadequately investigated. The latter is fought with great difficulties and only relatively recently was success attained in finding satisfactory approaches to the solution of this problem. The small blood vessels of the mesentery, the membrane of the brain, the sclera, the buccal sac of the golden hamster are accessible to direct observation, while in clinical practice the blood vessels of the occular fundus and the nailbed are accessible to direct observation. One can form indirect judgment of the microcirculation by the viscosity of the blood, the erythrocyte sedimentation rate, the rate of absorption of dyes or radioactive substances introduced into the tissues. Methodological difficulties in studying the microcirculation are great and quantitative estimation is possible only to a limited extent. Large errors are introduced by interpolation to the entire organism of data obtained in a small segment of tissues accessible to observation.

In the initial stage of blood loss the opening of the arterio-venous shunts occurs. As the result of spasm of the precapillary sphincters, a slight portion of the blood, passing the capillaries, enters the venules via anastomoses. Therefore there is a deterioration in the supply to a certain portion of the tissues, but then the return of blood to the heart and thus maintenance of the cardiac output is eased. Subsequently, under the influence of products of tissue metabolism, specifically histimene, there is expansion of the functioning capillaries and additional capillaries open, which over a certain period of time eases oxygen supply of the tissues. With a decrease of arterial pressure below 50 mm Hg, this adaptive reaction changes to a pathological one. Blood accumulates in the capillaries and there is a decrease in the rate of its movement; one observes pendulum-like movement, and in certain capillaries dense stasis begins. There is a decrease in the number of functioning capillaries (I. R. Petrov et al., 1969; Yu. M. Levin, 1966; Wiggers, 1950; Sweifach, 1958; Mellander, Lewis, 1963). Subsequently, one observes aggregation of erythrocytes and disruption of the ratio of plasma and of the formed elements. Certain capillaries seem almost entirely filled with plasma, while others are filled with aggregates of erythrocytes. In the latter stages, in certain capillaries, one observes blood clotting (microthrombi), which can serve as the cause of death for cells fed by these capillaries (Hardaway, 1965).

In the development of circulatory disorders, an initiating role is played by the neuro-reflex mechanism, particularly by stimulation of the sympathetic nervous system and excretion of catecholamines, followed by the local effect of products of deterioration and of biologically active amines which form in the tissues. The earlier treatment is begun and the more rapidly the necessary volume of tissue perfusion is restored, the easier it will be to eliminate microcirculatory disorders.

Disorders of Respiration, Gas Metabolism and the Acid-Alkali Balance

Hypoxia during blood loss is of a circulatory character and the degree to which it is pronounced depends upon the severity of hemodynamic disorder. With blood loss not exceeding 10 ml/kg, the consumption of oxygen is not disrupted and the rhythm of respiration is either stepped up or remains unchanged (R. A. Dymshits, 1958; Kho, Shoemaker, 1967). With subsequent blood loss there is a decrease in cardiac output, accompanied by a decrease in the consumption of /167 oxygen. The rhythm of respiration is disrupted and the oxygen-dissociation curve changes to the right, which eases the output of oxygen in the capillaries at a low partial pressure (Figure 42). There is a significant increase in the arterio-venous differential of oxygen both in volumetric percentages and in saturation percentages, which leads to an increase in the coefficient of tissue utilization of oxygen. According to the data of O. N. Bulanova (1966), in the mixed venous blood, with extremely severe blood loss, in place of 15-12% by volume oxygen, there is only 4-5% volumetric percent oxygen, and by the onset of agony even less. A low content of oxygen in the venous blood indicates that the tissues have not lost their capacity to consume oxygen and maximally remove it from the flowing blood. Saturation of the arterial blood with oxygen is maintained normally, which indicates preservation and even an increase in pulmonary ventilation. At the initial stages of blood loss, the increase in the arterio-venous differential compensates for the decrease in systemic oxygen transport, but subsequently, in connection with the strong decrease in cardiac output, consumption of oxygen falls and acute oxygen starvation develops. During this process, primarily, it is the central nervous system which suffers. According to the data of I. R. Petrov et al. (1966), during hypoxia of the brain there is disruption of the carbohydrate-phosphor metabolism. There is a decrease in the content of creatinphosphate and ATP. ADP accumulates, as do inorganic phosphorous and lactic acid; there is an increase in the content of ammonia. Similar changes were also detected in the heart muscle (Cho et al., 1966).

As is known, the basic force directing movement of oxygen from the capillary blood to the cells is the differential in partial pressure of molecular oxygen between the blood and the cell. This is why it is important to study such an index of oxygen supply of the tissues as the level of oxygen pressure (pO_2) in them. Changes in pO_2 during acute blood loss were studied in the blood, brain, heart, liver, stomach, intestine, and skeletal muscles (Ye. A. Kovalenko, V. B. Koziner, 1965; V. I. Korol'kov, V. B. Koziner, 1966; A. P. Krendel', I. M. Epshteyn, S. V. Yeliseyev, 1970; Yu. M. Levin, B. I. Slovikov, 1964; N. V. Sanotskaya, 1965). Certain characteristics in the change of pO_2 were noted which apparently reflect the character of blood supply in the regions studied. Thus, in the skeletal muscles pO_2 decreases more rapidly than does arterial pressure; pO_2 in the wall of the small intestine and stomach decreases in parallel with the arterial pressure, while breathing pure oxygen against a background of diminished arterial pressure (70-75 mm) enables one not only to attain but to exceed the original level of pO_2 (Figure 43). Only with a decrease in arterial pressure below 50 mm, breathing oxygen does not have an effect on the level of pO_2 in the tissues of the small intestine or stomach. In the cerebral cortex and in the subcortical ganglia of the brain, /168 a decrease in pO_2 was delayed in comparison with a decrease of arterial pressure, and this delay became more notable with a deep drop in arterial pressure. The boundary beyond whose limit severe changes occur in dogs was a blood loss in excess of 40 ml/kg. During this process arterial pressure decreases approximately 5 times, while pO_2 in the cortex and in the subcortical formations of the brain decreases by less than half. However, even in these cases compensation of pO_2 with temporary cessation of blood loss is possible. After the loss of 50 ml/kg and more, a preagonal state developed and pO_2 in the cortex and subcortex comprised about 50%. But even such profound changes can be reversible, and pO_2 in the brain can still normalize during pure oxygen breathing, as is shown in Figure 44. In this experiment, the cerebral cortex proved more sensitive both to oxygen deficiency and to an increase in its partial pressure in the inspired air.

Immediately after the death of the animal, pO_2 in the brain tissues does not always fall to zero. Similar data were obtained by D. B. Slavikov (1962), who observed that in the brain tissues at the onset of clinical death, pO_2 in a number of tests remained at a certain level, while pO_2 in the tissues of the liver always decreased to zero. The decrease of pO_2 in the myocardium occurs just as it does in the brain, however inhaling pure oxygen during high degrees of blood loss is ineffective and does not cause an elevation of pO_2 in the myocardium as it is observed to do in the brain tissues. A comparison of the changes in pO_2 in the tissues of the brain, myocardium and blood shows that the pressure of oxygen in the investigated tissues depends more on pO_2 in the venous blood than in the arterial blood. Thus, at the height of blood loss, with arterial pressure of 0-5 mm Hg, pO_2 in the arterial blood fell from 93 to 81 mm Hg, while in the venous blood it fell from 46 to 23 mm Hg. With a decrease in arterial pressure to 4-10 mm Hg in the myocardium, the coronary influx of blood and the cardiac consumption of oxygen were diminished by a factor of 3, while pO_2 decreased by only half. During this process pO_2 in the blood flowing from the coronary venous sinus also decreased by 50% (from 21 mm in the initial condition to 12 mm at the height of blood loss).

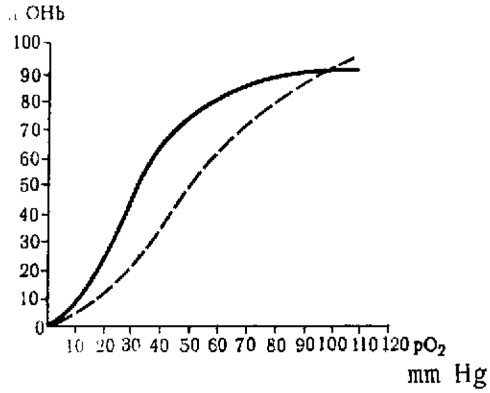

Figure 42. Curve of Oxyhemoglobin Dissociation (After G. V. Derviz). Heavy lined curve - norm; dashed curve - after blood loss.

Hypoxia of the tissues, developing during blood loss, leads to accumulation of inoxidized products in the organism and to the development of acidosis. In the initial stages of blood loss, blood pH does not change and acidosis is of a compensating character as the result of a decrease in pCO_2, primarily in the arterial blood. With an increase in blood loss, noncompensating metabolic acidosis develops with a decrease in pH and a drop in alkali reserves. According to our observations, in the preagonal condition, pH of the venous blood comprised 7.0-7.05, while in the arterial blood it was 7.17-7.20. A lower value of pH was recorded by O. N. Bulanova and I. O. Zaks during reanimation from death caused by blood loss (6.89 in the arterial blood and 6.85 in the venous blood). In the terminal stage of blood loss, with an arterial pressure near zero, a condition is observed in which acidosis of the venous blood is combined with alkalosis of the arterial blood. During this process, pH in the arterial blood does not change or slightly changes toward the alkali side, but there is a significant decrease in the content and pressure of carbon dioxide gas. The latter is due to increased ventilation of the alveoli, and by a decrease of pCO_2 in the alveoli, which leads to a significant increase in the respiratory coefficient. R. A. Dymshits (1958) observed an increase in the respiratory coefficient to 1.8, while G. V. Derviz et al. (1957) observed a decrease even to 2.8. However, hyperventilation is not the only cause of increased elimination of carbon dioxide gas. This same phenomenon is also observed in the case in which the animal is artificially supported by means of a constant volume of pulmonary ventilation. One of the basic and widely accepted indices of severity of hypoxia is the accumulation of unoxidized products in the tissues, as well as by a significant amount of accumulated lactic acid, pyroracemic acid and other organic acids. Moving from the tissues into the blood, it enters into reaction with the plasma bicarbonates, resulting in an increase in the formation and elimination of carbon dioxide gas. During blood loss, the content of sum organic acids in the blood increases in accordance with the severity of blood loss. According to the data of O. N. Bulanova (1966), at the end of lethal blood loss. According to the data of O. N. Bulanova (1966), at the end of lethal blood loss in the dog this index increases one and one-half times (from 11.2 ± 0.46 to 17.0 ± 0.73 mequv/l). During the treatment of uncomplicated blood loss, following restoration of the volume of circulating blood, the indices of the acid-alkali equilibrium after Astrup normalize following restoration of the hemodynamics and blood supply of the tissues, but the content of organic acids becomes higher, than at the end of blood loss, which is related to the washing of organic acids from the tissues. During very severe blood loss in people, /170 Ye. S. Zolotokrylina (1968) observed uncompensating metabolic acidosis in the first few hours and even days following blood loss. It is interesting that after a day the acidosis is replaced by alkalosis, and that the content of the very organic acids continued to remain heightened. In the most severe cases, terminating in death on the third to fourth day, a large amount of organic acids was observed in the blood (up to 40 mequv/l). Restoration of the acid-alkali balance took up to 20 days.

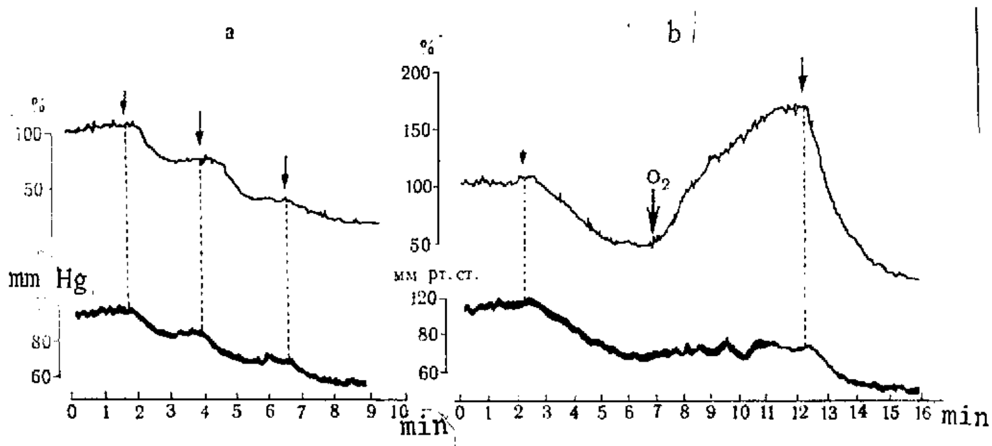

Figure 43. Changes in pO_2 in the Wall of the Small Intestine During Bleeding (a) and During Breathing with Pure Oxygen Against a Background of Bleeding (b). Experiment performed on the cat (after A. P. Krendal, I. M. Epshteyn, S. V. Yeliseyev). Arrows denote drop bleeding in the amount of 10-15 ml/kg. Lower curve - arterial pressure.

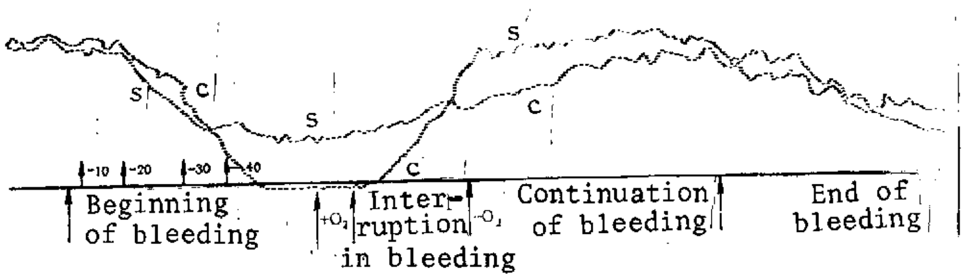

Figure 44. Selector Recording (By the Aid of a Commutation Device) of pO_2 in the Cerebral Cortex and Subcortex. Experiment performed on the dog (after Ye. A. Kovalenko and V. B. Koziner). From top to bottom: pO_2 in the cerebral cortex (C); pO_2 in the subcortex (S); zero line. During bleeding, oxygen pressure in the cortex falls lower than in the subcortex and at the end of blood loss is restored more rapidly. Figures with minus indicate the amount of blood removed.

Blood Changes

Thinning of the blood in response to blood loss is a well-known fact which is manifested in a decrease in the concentration of hemoglobin in the blood. The decrease in the volume of circulating blood caused by blood loss is compensated for by the organism by means of an influx of fluid from the intertissue spaces and by an influx of proteins dissolved in this fluid. It was demonstrated on splenectomized dogs that with removal of 56-57% of the original volume of blood, the volume of remaining blood measured at the end of blood loss comprised 50-55% and not 43-44% of the original level as one would expect. The increase against the calculated value was caused by dilution of the remaining blood by intertissue fluid passing into the circulatory system (Gregersen, 1959). According to the data of N. A. Gorbunova (1947), the volume of liquid fraction of the blood in dogs after loss of 25% of its volume is restored in half an hour, while the loss of 40% restored in two hours. The most intensive influx of fluid into the blood occurs in the course of the first hour and then slows. According to the data of R. A. Dymshits (1958), this reaction is not always proportional to the amount of lost blood; it is subject to individual fluctuations and is not uniformly pronounced in different animals. A relationship has been established between serum and tissue proteins and the dependency of plasma protein restoration at the expense of tissue protein reserves has been shown (N. A. Fedorov, 1947, 1961).

The regeneration of protein and their fractions was investigated in detail by V. M. Rodionov et al. (1957) in experiments performed on dogs with blood loss in the amount of 50-55 ml/kg; the dogs were maintained under life support by long-term infusion of Ringer's solution. After blood loss, restoration of the volume of circulating plasma occurs very rapidly and in the course of the first day the volume of plasma exceeds the original value, while on the third day it exceeds it by 30%. By this time, the compensation of protein comprises 85-90% of the original and the globulin fractions predominate. Restoration of proteins occurs in two phases: the first — more rapid (2-3 days) as the result of mobilizing the tissue resources, and the second — more slowly, as the result of increased synthesis of proteins in the liver. Total restoration occurs after 8-10 days. Denervation of the liver suppresses restoration of plasma proteins predominantly in the first phase. According to the data of N. A. Gorbunova (1964), restoration of blood proteins with respect to both albumins and to globulins, occurs in exactly the same fashion in splenectomized dogs after the loss of 25% of the volume of circulating blood as in the control animals. At the same degree of blood loss, D. M. Zubairov and V. I. Kurochkin (1964) did not detect differences with respect to the protein fractions of lymph and blood.

The participation of the hypothalamic region in the regeneration of proteins following blood loss was established. Thus, I. M. Bondarev (1959) observed restoration of the serum proteins and their fractions by the third day following blood loss of 45-50 ml/kg in dogs with destroyed hypothalamic centers, while in the controls with the same degree of blood loss this occurs by the tenth day. Most investigators consider that restoration of the volume of circulating blood /171 in plasma proteins occurs continuously. Somewhat unusual data were obtained by Swan (1965).

In experiments carried out on dogs with loss of 35% of the blood volume he found that the maximum influx of fluids into the blood vessels occurs in the first one and one-half hours, then it inversely proceeds to the tissues and three hours later the plasma volume becomes the same as it was after blood loss, although the arterial pressure and the hematocrit index are restored to the original figure.

The proteins which are passed into the circulatory system after blood loss have a qualitative difference in comparison with the normal serum proteins. This is apparent from the fact that the colloid-osmotic plasma pressure is restored more rapidly than the concentration of serum proteins. Hence, in the first days following blood loss proteins enter the circulatory system which have a heightened colloid-osmotic activity, indicating their great dispersion (N. A. Messineva, 1952; V. B. Koziner, 1961). With repeated, small blood losses in rabbits, structural changes in the serum proteins are observed; there is a decrease in their temperature stability and one-time blood loss does not influence this index (Yu. M. Madiyevskiy, 1961).

A number of factors influence the reinforced influx of fluid into the bloodstream. As a result of blood loss, there is a drop in blood pressure, particularly in the venous terminus of the capillary, and hydrostatic pressure in it becomes less than oncotic pressure of proteins in the plasma, which is caused by the movement of fluid from the tissues to the blood. Blood loss activates the system hypophysis-adrenal cortex. There is an increase in the secretion of aldosterone, which strengthens reabsorption of sodium in the proximal region of the renal canaliculi. Retention of sodium leads to reinforced reabsorption of water in the canaliculi and to a decrease in urine formation.

There is an increase in the passage of water from the tissues to the blood. There is a simultaneous increase in the blood content of antidiuretic hormone of the posterior lobe of the hypothesis. Hydrocortisone also has great significance in response to blood loss. In experiments carried out on adrenalectomized dogs with blood loss of 20% of the volume of blood, success was attained in supporting the life of the animals and normal restoration of the volume of blood was managed with administration of adequate doses of deoxycorticosterone and cortisone (Marks et al., 1967). According to the data of McNeil et al., (1963), the administration of hydrocortisone and aldosterone increases mobilization of tissue fluid. The passage of fluid from the tissues into the blood also enables an increase in permeability of the vascular membrane in the direction of the vascular tree. There are data concerning an increase in the suction capacity of the abdomen as a result of blood loss, but transfusing blood normalizes suction (I. L. Bregadze et al., 1960).

An increase in the blood content of the enzyme aspartate-aminotransferase in dogs following blood loss has been described. The authors explain this by influx of the enzyme from the tissues as the result of disrupted permeability (N. A. Kulikova, V. N. Kudrin, M. V. Assur, 1968). After blood loss, there is an increase in the blood's content of sugar, and denervation of the liver does not eliminate this phenomenon (R. A. Dymshits, 1958). The development of hyperglycemia is made possible by stimulation of the sympathetic nervous system, by increased secretion of adrenaline and by an increase in the blood's content of glucocorticoids.

As the result of a decrease in arterial pressure, the juxtaglomerular apparatus of the kidneys increases its secretion of renin and the content of renin in the blood can increase up to five times, in comparison with the original level. The secretion of renin is brought about reflexly by the sympathetic nervous system, via the baro- and kemo-receptors located in the kidneys. Renin enables restoration of the volume of circulating blood and arterial pressure. It forms angiotensine, which constricts the blood vessels /172
and stimulates the secretion of aldosterone (MacKenzi et al., 1966; Lister et al., 1966; Scornic, Polodini, 1964; Win, Lister, 1966). However renin--angiotensine, in making possible an increase in the volume of circulating blood,

does not play a role in the distribution of blood throughout the organs following blood loss (Tacacs, 1965).

Under the influence of blood loss there are changes in the immune properties of the serum. For a short time, several hours, there is a decrease in the titer of the complement, precipitins and agglutins. There is an increase in phagocytic activity of the leucocytes (R. A. Dymshits, 1958). An increase in the titer of normal antidysenteric antibodies in rabbits has been described after blood loss of 20 ml/kg, and among people, active donors. Among rabbits immunized with the Flexner dysentery vaccine, one-time bleeding increased the production of antibodies fourfold (M. V. Zemskov et al., 1964, 1965).

A long well-known fact is the increased coagulation of the blood which occurs after blood loss, notwithstanding a decreased number of thrombocytes and a decrease in the content of fibrinogen. Simultaneously, fibrinolysis is activated, which was noted in experimental studies and in clinical observations (A. S. Kukel' et al., 1969; Bergents, Nilsson, 1961; Bonvier et al., 1964).

The rate of lymph coagulation does not change (D. M. Zubairov, V. I. Kurochkin, 1964). An increase in the fibrinolytic activity of the blood can be evaluated as a manifestation of the protective reaction in response to an increase in the overall coagulating activity (K. N. Gorelov, 1967), however the passage into the blood of fibrinolytic agents together with the tissue fluid is also possible. An increase in the tonus of the sympathetic nervous system and heightened secretion of adrenaline doubtlessly enable accelerated coagulation of the blood during blood loss. Here, great significance attaches to changes in the components of the coagulating system. According to the data of D. M. Zubairov (1962), during acute blood loss an increase in the adhesiveness of thrombocytes occurs, as well as an increase in the consumption of prothrombin, the concentration of thrombine, content of the VIII factor, and there is a decrease in the antihemophilic globulin. The most probable reason for an increase in the activity of the coagulating system is considered by that author to be an influx of tissue thromboplastin or a decrease in the anti-coagulating factors.

After massive blood loss in dogs (40% of the volume of blood), V. P. Baluda and N. A. Gorbunova (1961) found an increase in thromboplastin activity as the result of an influx of tissue fluid into the bloodstream and a twofold decrease of antithromboplastin activity. The latter is considered by these authors to be caused by more difficult secretion of heparin from the mast cells under conditions of vascular spasm and elimination of the antiheparin factor from the deteriorated erythrocytes.

As was noted above, as the result of blood loss there is a decrease in the amount of thrombocytes, but the restoration of the thrombocyte level occurs very rapidly. Posthemorrhagic leucocytosis has been described and is well--known; this occurs in two phases: leucopenia with relative lymphocytosis and subsequent neutrophilic leucocytosis. Leucocytosis at first has a redistributing character, but then is caused by activation of hemopoeisis, which is indicated by change in the leucocytic formula to the left. The number of erythrocytes in the content of hemoglobin decrease in accordance with the severity of blood loss, and a leading role is played by the degree of dilution of the blood by the intertissue fluid. Determination of the absolute content of the volume of all erythrocytes (in milliliters) remaining in the blood stream is most valuable.

The minimum concentration of hemoglobin compatible with life under /173
conditions of restoring the blood volume is about 3 g% (V. B. Koziner, Ye. A. Kovalenko, 1964; Johansen, Laver, 1966).

The absolute number of erythrocytes continues to decrease and in the post-hemorrhagic period, which was first established by Ya. G. Uzhanskiy et al., in the laboratory of A. A. Bogomolets (1949). An increase in the breakdown of erythrocytes is also observed among donors following the removal of blood from them. A study of the length of lifespan of the erythrocytes themselves in dogs which had endured blood loss of 30-40 ml/kg was carried out by N. A. Fedorov and N. A. Gorbunova (1963) by the aid of radioactive chromium (Figure 45). Curve 1 shows the half lifetime of erythrocytes among healthy dogs, curve 2 after blood loss. Three populations of cells with different lifetimes are clearly shown; the lifetime is significantly shorter than among normal animals. Breakdown of erythrocytes proceeds more intensively the more intense blood loss is. It was shown that the serum of dogs which had endured blood loss has hemolytic properties. These properties are manifested 24 hours after blood loss and continue for 5-7 days. The basic location of erythrocyte breakdown is the spleen, which was shown by N. A. Gorbunova (1965, 1966, 1967) on splenectomized dogs. Ya. G. Uzhanskiy (1968) advanced a hypothesis to the effect that as the result of blood loss antibodies to one's own erythrocytes appear. It was later shown that immature cells entering the blood after blood loss bear or adsorb proteins under surfaces which, reacting with antiglobulin, leads to a positive direct Coombs' test (N. A. Fedorov et al., 1966; Ye. A. Zotikov et al., 1968). V. I. Levin (1969) negates the immunological nature of erythrocytic destruction and assigns the main role to an increase in the content of the hemolytic agent lysolecithin in the blood and to an increase in metabolic processes in the erythrocytes. The breakdown of erythrocytes after blood loss is viewed by Ya. G. Uzhanskiy (1968) as an important factor for increasing regeneration of the blood; products of deterioration of mature erythrocytes have a stimulating effect on erythropoeisis while at the same time products of deterioration of reticulocytes inhibit it. The stimulating effect of hemolysate on erythropoeisis has been shown by direct experiments (B. A. Serebryanaya et al., 1969). However, this effect could be intermediary.

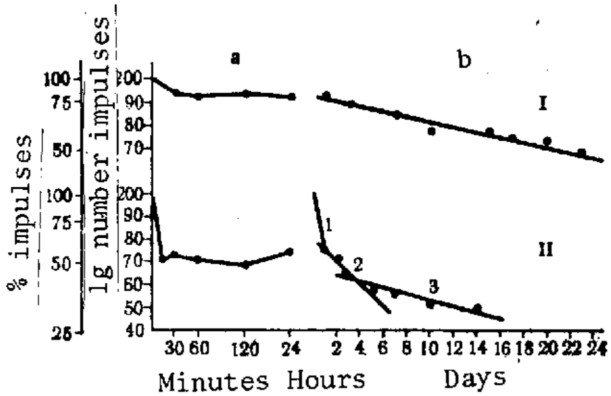

Figure 45. Change in the Period of Half Life of Labeled Erythrocytes of the Dog After Acute Blood Loss (After N. A. Fedorov and N. A. Gorbunova). a, Percentage of original labeled erythrocytes circulating in the vascular tree in the time interval 15 minutes - 24 hours after introduction; b, T 1/2 labeled erythrocytes; 1, 2, 3, T 1/2 various populations of cells. I, Test 44; II, Test 12.

More than 60 years ago it was shown that the blood serum of animals which had endured blood loss contains special substances — hemopoeitins which activate red cell growth and which hasten maturation of erythrocytes (Carnot, Deflandre, 1966). It has now been established that there are erythropoeitins which activate red cell /174 growth of the bone marrow and leucopoeitins which activate white cell growth. The study of erythropoeitins has recently been developed in works of N. A. Fedorov and his co-workers. It has been shown that in the first hours following blood loss the content of erythropoeitins sharply decreases, and after 5 hours begins to increase. The greatest content is observed at the first and fifth days, and the first peak is linked with hypoxia, while the second coincides with the reticulocytic crisis in the peripheral blood and the activation of bone marrow.(M. G. Kakhetelidze, N. A. Fedorov, 1961; M. G. Kakhetelidze, Ye. M. Makarova, 1962; G. P. Moskaleva et al., 1970; L. I. Timoshenko, 1964). In donors, particularly specialist donors, hemopoeitic activity of the serum increases 24-48 hours after giving blood (P. M. Al'perin et al., 1968). D. I. Bel'chenko and Yu. V. Zinov'yev observed an increase in hexokinase activity of the myelokariocytes in dogs after blood loss of about 30 ml/kg and hypothesize that this phenomenon is related to the hemopoeitic activity.

Compensator Mechanisms

In the course of acute blood loss there is a progressive decrease in the volume of circulating blood and hypoxia increases. The volume of blood flow through the organs, in accordance with the oxygen requirements of the tissues, primarily of the brain and heart, in the regulating parameter of the compensator processes which are directed toward maintaining the necessary level of oxygen supply. In the struggle with circulatory hypoxia, the organism has at its disposal the following capacities: 1) redistribution of the blood with a decreased volume of circulating blood and maintenance of the blood flow in vitally important organs at the expense of the skin, the digestive organs, and possibly, the muscles; 2) restoration of the volume of circulating blood as the result of an influx of intertissue fluid into the vascular tree; 3) an increase in cardiac output and coefficient of oxygen utilization with restoration of volume of the circulating blood. As a whole, the process is directed to converting circulatory hypoxia to anemic hypoxia, which is less dangerous and more easily compensated for. In accomplishing the compensator reactions, neural, endocrine, and tissue factors participate. The higher regions of the central nervous system suffer earliest, and the unconditioned reflexes are maintained longest (V. A. Negovskiy, 1966). According to the data of I. R. Petrov and his school, pressor and depressor vascular reflexes are at first strengthened and then undergo phase changes indicating the appearance of

inhibition in the vasomotor center. The cardiac and vascular reactions which lead to redistribution of the blood appear reflexively upon stimulation of the receptor zone (sinocarotid and aorta). Stimulation of the sympathetic nervous system leads to spasm of the arterial blood vessels and to tachycardia. There is an increase in the function of the anterior lobe of the hypophysis and of the adrenals. There is an increase in the secretion of catecholamines and an increase in the blood's content of aldosterone, renin, and angiotensine. The hormonal effects support vascular spasm and alter the permeability of the blood vessels, making possible the influx of fluid into the vascular tree. A decrease in blood flow in the tissues leads to tissue oxygen starvation, as the result of which the liberation of energy is partially redirected to the anaerobic glycolysis pathway. As the result of accumulation of unoxidized products, the pH changes to the acid side. There is an increase in the concentration of glutathione in the erythrocytes. Glutathione is an activator of a number of enzymes and a reserve of the active SH groups; it also causes a change in the /175
acid-dissociation curve to the right and thereby eases detachment of oxygen and the lowest of its partial pressures. Besides this, in the tissues biologically active substances are accumulated making possible change in the lumina of the blood vessels and change in their permeability.

One can isolate several stages in the development of blood loss, each of which is characterized by a certain degree of hypoxic disorders related to disruption of circulation.

In young, healthy people blood loss of 500 and even 1,000 ml does not cause significant hemodynamic changes. In donors one observes only a rapidly passing increase in pulse frequency. Rapid compensation is achieved by redistribution of blood, and interstitial fluid begins to pass into the blood stream at an initial rate of 100 ml/hour. Subsequently, the rate of passage of fluid slows and the volume of blood is restored to the norm in a period of 18-48 hours (Juchems, Ammerschlager, 1967; Moore et al., 1966). The passage of fluid into the vascular tree occurs in two phases. In the first phase (limited by the time of blood loss) nonprotein bearing fluid enters the vascular tree and is soon eliminated by the kidneys. The second phase occurs in 2-24 hours; the volume of plasma during this phase is restored by intertissue fluid containing protein (Doberneck, Zimmerman, 1964).

Data on the possibility of compensating for various degrees of blood loss were obtained in experiments carried out on dogs. In the initial period of blood loss (up to 30 ml/kg), the severe hypoxic phenomena are absent and disorders caused by blood loss are successfully compensated for by the organism independently. Arterial pressure is slightly lowered and the heart reacts by tachycardia with a correct sinus rhythm. The coronary blood flow does not significantly change and blood pressure in the brain tissues is decreased, but with temporary cessation of blood loss is rapidly restored to original values. Respiration deepens and becomes more frequent. There is a very clear-cut and unique blood supply of the vitally important organs (brain and heart). At the same time as the tonus the blood vessels of the muscles, intestines and kidneys increases, tonus of the coronary blood vessels decreases making possible preservation of the previous level of coronary blood flow in spite of the decrease in arterial pressure which has begun. In the brain one also notes a decrease in tonus of the arterial portion of the capillaries. During short-term cessation of blood loss the volume and pulsation of the brain is rapidly restored and, as a reflection of this process, the level of oxygen pressure in the brain is also restored.

Prognosis at the given stage of blood loss is favorable and only minimum aid is necessary to eliminate its consequences. Survival is possible without treatment.

With continuing blood loss the processes of compensation are disrupted. With blood loss of 40 ml/kg, arterial pressure decreases by approximately 5 times, the rhythm of cardiac contractions slows and various disorders of conductivity changes in the value and direction of spikes appear on the EKG; the volume of coronary blood flow begins to diminish, pathological forms of respiration appear, the pressure of oxygen in brain tissues is approximately 60% of the original value. There is a decrease in oxygen pressure in the mixed venous blood. However, even in this condition compensation for the brain's oxygen supply is possible, which is manifested in elevation of oxygen pressure and in its tissues with temporary cessation of blood loss. Independent restoration of hemodynamics and respiration at this stage of blood loss is /176 possible only in rare cases. Replacement of lost blood even by poorly effective transfusion means leads to recovery from this condition.

Blood loss of 50 ml/kg or more is characterized by the development of severe disorders of circulation and respiration. Arterial pressure comprises no more than 10% of the original level notwithstanding maximum increase in vascular tonus. Bradycardia develops and the EKG registers severe disorders in rhythm and conductivity and the volume of coronary blood flow significantly decreases. Periodic respiration appears. The pressure of oxygen slightly decreases in the arterial blood and very clearly decreases in the venous blood; pH of the blood changes to the acid side and consumption of oxygen and elimination of carbon dioxide gas decreases, but not to an identical degree. The respiratory coefficient becomes greater than 1. Tension of oxygen in the brain tissues comprises about 50% of the original level. Independent restoration of the disrupted functions is impossible.

With a decrease in arterial pressure to zero the preagonal and agonal conditions begin which are characterized by subsequent deepening of the described disorders and by complete disintegration of the circulatory and respiratory systems. Pressure of oxygen in the brain tissues, cardiac muscle and mixed venous blood falls to 50%. Apparently, this level of oxygen pressure in the brain tissues is the boundary between life and death; a subsequent decrease in oxygen pressure in the brain leads to rapid death, independent of the cause of hypoxia. However even at this stage of circulatory hypoxia, replacement of lost blood and restoration of the volume of circulating blood even by the aid of fluids not containing erythrocytes can still save life.

With very great blood loss, and particularly with rapid loss of blood, the compensator mechanisms can be inadequate or do not succeed in activating and death ensues. With inadequacy of compensator mechanisms and during long-term decrease in arterial pressure acute blood loss changes to an irreversible condition lasting for hours and not subject to treatment by blood transfusion. The irreversible condition as the result of long-term blood loss (oligemic or hemorrhagic shock) differs in many indices from acute blood loss and approaches the terminal stage of shock of other origin. Here the hemodynamics progressively deteriorate as the result of the appearance of a defective circuit, whose development can proceed along several channels. Blood decreases oxygen transport which leads to a decrease in the consumption of oxygen by tissues and to accumulation of oxygen debt, as the result of oxygen starvation the contractive function of the myocardium is weakened, there is a fall in the minute volume, which in their turn even further deteriorate oxygen transport. Another pathway of development of the defective circuit is the following: as the result of a decrease in oxygen transport, the central nervous system suffers and there is disruption in the function of the vasomotor center; the vasomotor reflex is weakened and function incorrectly; the latter leads to an even greater fall in pressure and to a decrease in cardiac output, which in turn leads to subsequent deterioration of the regulating effect of the nervous system, deterioration of the hemodynamics and decrease in oxygen transport. If this faulty circuit is not righted, the accumulating disorders can lead to death. I. R. Petrov (1967) considers the term "irreversible blood loss" to be incorrect, since improved methods of treatment make it possible to save life in cases earlier considered to be hopeless and therefore he suggests substituting that term with "stage of exhaustion".

Experimental Therapy of Acute Blood Loss /177

The therapy of acute blood loss is based upon strengthening or imitating mechanisms of compensation which the organism uses in combating this harmful state. Unquestionably, the best method for liquidating both circulatory and anemic hypoxia will be transfusion of compatible blood. In addition to this, blood replacements are widely used. Their application is based on the fact that the loss of plasma and the associated decrease in volume of circulating blood is endured much more poorly than loss of erythrocytes. Thus, survival is still possible with maintenance of a total of 35% of the initial number of erythrocytes, while at the same time loss of more than 30% of the initial volume of plasma entails a lethal danger. For treating blood loss, solutions of high molecular colloids, whose physical-chemical properties are nearer the properties of plasma, are used. The most widespread use is that of dextrane preparations (the Soviet preparation is polyglucine), as well as preparations of gelatin (Soviet preparation — zhelatinol'), and polyvinylpyrrolidone, which is less widely used. Abroad, hydrooxyethyl starch is being studied, and in recent years interest has grown in complex saline solutions. Blood replacing substances have been reported in greater detail in the special literature

(I. R. Petrov et al., 1969; I. R. Petrov, A. N. Filatov, 1963; A. Ye. Kiselev et al., 1969; A. A. From, V. B. Koziner, 1969). In many countries, including the USSR, work is underway to obtain a blood-replacing substance capable of transporting oxygen (G. Ya. Rozenberg, 1970).

Although great successes have been attained in the treatment of blood loss, investigations in this field have not stopped. The results can be compared only in a case in which these investigations are conducted under identical maximally standardized conditions. From the systematic survey of conditions of the circulation and respiration given above, one can see that the animal organism successfully compensates for the effects of blood loss. Only in a case in which oxygen pressure in the brain tissues falls lower than 60-50% of the original level does breakdown in the compensator mechanisms occur. The treatment of blood loss prior to the onset of this breakdown even with substances not fully restoring the volume of the circulating blood will always yield a positive effect, since at this moment minimum aid is sufficient to restore oxygen supply of the tissues. Carrying out treatment under conditions of an inadequate degree of blood loss, when regulation has not been disrupted, is the reason for unjustifiably high estimation of certain blood replacing substances and for the subsequent difference of results when the solutions under study were investigated under more severe conditions.

Observation of the condition of the animal should not be limited to the first minutes after the conclusion of treatment, since this picture of revival and strengthening of functions of circulation and respiration is observed nearly always, even during treatment with poorly effective substances. Subsequent course of post-transfusion period depends upon how firmly the volume of circulating blood has been restored. Therefore, great significance attaches to investigations conducted 2-3 hours after blood replacement and in the days subsequent blood replacement. In the experiments of G. V. Derviz et al., (1957), lethal blood loss in dogs was staved off by a heteroprotein blood replacer. During this process, the volume of circulating blood 2 hours later was only 75% of the original level. As a result of this the influx of blood to the heart was diminished in the minute volume did not increase to the necessary extent. Arterial pressure also did not return to the original values. Although in this experiment oxygen consumption reached the norm, its subsequent increase was not possible, since oxygen pressure in the venous blood /178 decreased to shock values and any additional load would have proved fatal. This example is typical for all cases of blood loss when the volume of circulating blood is not fully restored.

Medicinal therapy eases symptoms but does not eliminate basic causes. For example, preparations which heighten vascular tonus, particularly pressor amines, are contraindicated until the full volume of blood is restored. Increasing vascular spasms, they only deepen hypoxia (Ye. S. Zolotokrylina, 1966; Wickerson, 1962). Blockade of the sympathetic nervous system with phenoxybenzamine leads to decrease in the volume of circulating blood and to a drop in cardiac output during acute blood loss (Nagy et al., 1965), when as with protracted blood loss (irreversible hemorrhagic shock) phenoxybenzamine increases the viability of animals (Nickerson, 1962). The application of ganglion blocking hexamethonidine with blood loss worsened tissue restoration and increased the content of products of anaerobic glycolosis, in comparison with the control (O. T. Denisov, 1965; Danoff, Gree, 1964). According to the data of I. R. Petrov, to eliminate oxygen deficiency it is expedient to employ breathing oxygen and mixtures of oxygen with 3-5% carbon dioxide.

With extremely severe blood loss, breathing pure oxygen produces only short-term increase in oxygen pressure in the brain tissues (Ye. A. Kovalenko, V. B. Koziner, 1965), while breathing a mixture with an increased content of oxygen (up to 45%) does not protect the myocardium from severe hypoxic disorders (V. I. Korol'kov, 1966). Taking into account the fact that it is primarily the central nervous system which suffers from oxygen deficiency, I. R. Petrov (1967), by means of cooling the heads of experimental animals, lowered the oxygen requirement of the brain and thereby delayed the onset of irreversible changes caused by blood loss.

In addition to the described conditions, one should also take into account other conditions which influence the effectiveness of treating blood loss, but restoring the volume of circulating blood will always remain mandatory.

REFERENCES

Abel, F. L. and Q. R. Murphy, "Mesenteric, Renal, and Iliac Vascular Resistance in Dogs After Hemorrhage," *Am. J. Physiol.*, Vol. 202, p. 978, 1962.

Allen, T. H., R. A. Walzer and K. Gregersen, "Blood Volume, Bleeding Volume and Tolerance to Hemorrhage in the Splenectomized Dog," *Am. J. Physiol.*, Vol. 196, p. 176, 1959.

Amashukeli, G. V., "Circulatory Changes in the Brain During Hemorrhages and Blood Transfusions," *Pat. Fiziol.*, Vol. 3, p. 29, 1969.

Baluda, V. P., "The System of Hemostasis of the Healthy Organism and During Hemorrhages," in the book: *Tezisy Dokl. 12-Go Mezhdunarodnogo Kongressa po Perelivaniyu Krovi* [Abstracts of Reports of the Twelfth International Congress on Blood Transfusion], Moscow, p. 288, 1969.

Barmina, Ye. F., "Protein Synthesis and RNA Synthesis in the Liver of the Rabbit After Blood Loss," *Byull. Eksper. Biol.*, Vol. 10, p. 23, 1968.

Cho, Y. W., D. M. Avido and S. Bellet, "Myocardial Metabolic Changes During Acute Hemorrhage," *Angiology*, Vol. 16, p. 532, 1966.

Danoff, D. S. and N. M. Green, "Vasodilation and the Metabolic Response to Hemorrhage," *Surgery*, Vol. 55, p. 820, 1964.

Dymshits, R. A., *Ostraya Krovopoterya* [Acute Blood Loss], Chelyabinsk, 1958.

Fedorov, N. A. and N. A. Gorbunova, "Study of the Duration of Life of Erythrocytes of the Dog During Acute and Chronic Blood Loss," *Pat. Fiziol.*, Vol. 6, p. 65, 1963.

Gorbunova, N. A., "Duration of Half Life of Erythrocytes Cr^{51} in the Dog with Various Severe Blood Losses," *Pat. Fiziol.*, Vol. 2, p. 58, 1968.

Gorelov, K. P., "Functional Condition of the Anticoagulation System Under Conditions of Blood Loss," *Vopr. Med. Khimii*, Vol. 1, p. 5, 1967.

Gurevich, I. B. and M. L. Garfunkel', "Changes of the Heart During Acute Blood Loss," *Pat. Fiziol.*, Vol. 6, p. 39, 1959.

Juchems, R. and G. Ammerschlaeger,

Kho, L. K. and W. C. Shoemaker, "Cardiorespiratory Changes in Acute Hemorrhage," *Surg. Gynec. Obstet.*, Vol. 124, p. 826, 1967.

Kovalevskiy, G. V., "Shunning of Renal Blood Flow During Blood Loss, Experimental Investigation," *Arkh. Pat.*, Vol. 2, p. 24, 1963.

Kovalenko, Ye. A. and V. B. Koziner, "Oxygen Supply of the Brain During Circulatory Hypoxia," *Fiziol. Zh. SSSR*, Vol. 5, p. 547, 1965.

Krendal, A. P., I. M. Epshteyn and S. V. Yeliseyeva, "Oxygen Pressure in the Wall of the Stomach, Small and Large Intestines in the Norm and in Pathology," *Pat. Fiziol.*, Vol. 1, p. 29, 1970.

Kulagin, V. K., "Pathogenetic Fundamentals of Therapy of Shock and Blood Loss by Corticosteroids and ACTG," *Voyen.-Med. Zh.*, Vol. 12, p. 7, 1964.

Kulikova, N. A., V. N. Kudrin and M. V. Assur, "Comparative Characteristics of Changes in the Activity of Aminotransferase of the Blood During Experimental Traumatic Shock and Blood Loss," *Pat. Fiziol.*, Vol. 1, p. 31, 1968.

Levin, Yu. M. and B. I. Slovikov, "Oxygen Pressure and the Hemodynamics of the Brain During Lethal Blood Loss and Subsequent Revival (In Experiment)," *Byull. Eksper. Biol.*, Vol. 12, p. 27, 1964.
Lister, J., M. S. Win and R. P. Altman, "Factors Influencing Homeostatic Responses to Hemorrhage," *Surgery*, Vol. 60, p. 43, 1966.
Markin, S. P. and V. P. Strekalovskiy, "Surgical Blood Loss and Pathological Deposition of Blood," *Khirurgiya*, Vol. 12, p. 25, 1967.
Marks, L. J., D. W. King and H. F. McCarthy, "Physiological Role of Cortisol in the Plasma Volume Response to Hemorrhage," *Surgery*, Vol. 61, p. 422, 1967.
Mchedlishvili, G. I., *Funktsiya Sosudistykh Mekhanizmov Golovnogo Mozga. Ikh Rol' v Regulirovanii i v Patologii Mozgovogo Krovoobrashcheniya* [Function of Vascular Mechanisms of the Brain. Their Role in Regulating and in the Pathology of the Brain's Circulation], Leningrad, 1968.
McKenzie, J. K., M. R. Lee and M. F. Cook, "Effect of Hemorrhage on Arterial Plasma Renin Activity in the Rabbit," *Circulat. Res.*, Vol. 19, p. 269, 1966.
Moskaleva, G. P., B. A. Serebryanaya and N. A. Gorbunova, "Dynamics of Erythropoeitense After Acute Blood Loss in the Dog," *Pat. Fiziol.*, Vol. 1, p. 68, 1970.
Negovskiy, V. A., "Pathophysiological Principles of Extinction and Restoration of Vital Functions of the Organism," in the book: *Osnovy Reanimatologii* [Foundations of Reanimatology], Moscow, p. 6, 1966.
Neutze, J. M., E. Wyler and A. M. Rudolph, "Changes in Distribution of Cardiac Output After Hemorrhage in Rabbits," *Am. J. Physiol.*, Vol. 215, p. 857, 1968.
Pavlov, A. D., "Change in the Synthesis of RNA and Protein in the Kidneys During Post-Hemorrhagic and Phenylhydrasine Anemia," *Pat. Fiziol.*, Vol. 6, p. 45, 1969.
Petrov, I. R., V. A. Bondina and Ye. A. Senchilo, *Plazmozameshchayushchiye Rastvory Pri Lechenii Krovopoteri i Shoka* [Plasma Replacing Solutions During the Treatment of Blood Loss and Shock], Leningrad, 1969.
Sanotskaya, N. V., "Change in Oxygen Pressure in the Tissues During Acute Blood Loss and During Subsequent Restoration of the Volume of Circulating Blood," *Fiziol. Zh. SSSR*, Vol. 10, p. 1220, 1965.
Scornic, O. A. and A. C. Paladini, "Angiotensin Blood Levels in Hemorrhagic Hypotension and Other Related Conditions," *Am. J. Physiol.*, Vol. 206, p. 553, 1964.
Skillman, J. J., D. P. Lauler and R. B. Hickler et al., "Hemorrhage in Normal Man: Effect on Renin, Cortisol, Aldosterone and Urine Composition," *Ann. Surg.*, Vol. 166, p. 865, 1967.
Swan, H., "Experimental Acute Hemorrhage. The Relation of Blood Pressure Change to Plasma Dilution," *Arch. Surg.*, Vol. 91, p. 390, 1965.
Treeman, J., "Physiological Effects of Hemorrhage," *Roy. Coll. Surg.*, England, Vol. 33, p. 138, 1963.
Uzhanskiy, Ya. G., *Fiziologicheskiye Mekhanizmy Regeneratsii Krovi* [Physiological Mechanisms of Blood Regeneration], Moscow, 1968.
Voronyanskaya, L. G., A. V. Zav'yalov and B. I. Kuznik, "The Mechanism of Development of Hypercoagulation During Acute Blood Loss," *Byull. Eksper. Biol. i Med.*, Vol. 3, p. 35, 1967.
Win, M. S. and J. Lister, "Role of the Kidney and Adrenaline in Homeostatic Response to Hemorrhage," *Surg. Forum*, Vol. 17, p. 21, 1966.

Zemskov, M. V., N. V. Zhuravleva and S. A. Ignat'yeva, "Stimulating Formation of Post-Vaccination Antibodies by Bleeding," *Byull. Eksper. Biol.*, Vol. 3, p. 72, 1965.

Zolotokrylina, Ye. S., "Characteristics of Changes of the Acid-Alkali Balance in Patients After Lethal (By Volume) Blood Loss and Multiple Injuries," *Vestn. Khir.*, Vol. 4, p. 11, 1968.

Translated for the National Aeronautics and Space Administration under Contract No. NASw-2485 by Techtran Corporation, P.O. Box 729, Glen Burnie, Maryland, 21061. Translator: Samuel Blalock, Jr.